UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/205,658	12/03/98	RUVKUN G	00786/351004

EXAMINER	
KAUSHAL S	
ART UNIT	**PAPER NUMBER**
1633	19

HM22/0328

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DATE MAILED: 03/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/205,658	Applicant(s) RUVKUN ET AL.	
	Examiner Sumesh Kaushal	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,10-23 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-5,8,10-17,23 and 25-28* is/are allowed.

6)☒ Claim(s) *18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 01/10/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09205658 is acceptable and a CPA has been established. An action on the CPA follows.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

2. Claims 18-22 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use the invention**, for the same reasons of record as set forth in the official action mailed on 01/10/00.

The claims 18-19 are drawn to a method of diagnosing impaired glucose tolerance condition, obesity or propensity thereto and longevity in a patient by analyzing the levels of PTEN expression or activity in patient samples. The claims 20-22 are drawn to a method of ameliorating or delaying the onset of impaired glucose tolerance condition and increasing longevity in a patient by administering a therapeutically effective amount of a compound that modulates the PTEN expression or activity.

3. Applicant's arguments and Dr. Gary Ruvkun declaration filed on 02/05/01 have been fully considered but they are found not persuasive. Dr Ruvkun's declaration teaches the making of a transgenic nematode (*C. elegans*) wherein the PTEN transgene rescue a daf-18 mutant at level of 100% (response, page 12 table-1). The applicant argues (in view of Nakashima et al) that excess of PTEN activity leads to inappropriate insulin signaling in mammalian cells as indicated

in the instant specification (response, pages 13-15). The applicant further argues (in view of Iida et al) that human patient carrying a hetrozygous PTEN gene mutation results in hypersensitivity to insulin that exhibits rapid clearance of blood glucose (response, pages 13-15). The applicant concluded that because PTEN plays a role in mammalian insulin signaling, therefore it is involved in impaired glucose tolerance conditions in mammals. The applicant further argues that PTEN is a daf-18 homolog and is expected to regulate fat accumulation in mammals (response, page 16). The applicant further argues that data in table-I show that PTEN increases longevity in C.elagans due to functional similarity with Daf-18.

However, this is not found persuasive because various factors govern the development of impaired glucose intolerance or obesity. Obesity is a complex phenotype, which is not only the result of genetic variations but is also the out come of personal behavioral and life style. The art a the time of filing teaches that body weight is physiologically regulated and the storage of fat provides signals to the brain that makes the subject eat less and burn more fuel. One of the molecule that is involved in such signaling is the obese (ob) gene products. A mutation is ob gene results in profound obesity and type II diabetes. Furthermore, the expression of human ob gene is markedly higher in adipose tissues of massive obese subjects (Lonnqvist et al Nat. Med. 1(9):950-953, 1995, abstract, page 951 col.1 para.1, fig-2, table-1, *ref of record*). In addition, the development of impaired glucose intolerance involves both hyperlipidemia and the dietary fat composition, which also depends upon personal dietary habits (Zeman et al, Atherosclerosis, 134(1-2):318, 1997, *ref of record*). Thus, considering the complexity and role of individual genes in impaired glucose intolerance or obesity, it is unclear how the one skill in the art would conclude that administration of a compound that decrease PTEN expression or activity would result in the amelioration or delaying of impaired glucose tolerance condition or obesity, wherein the condition is not governed by PTEN. For example, it is unclear how an individual with a mutation in ob gene would benefit from the administration of a compound that modulates PTEN expression.

Furthermore, the therapeutic use of a compound that modulates longevity in C.elegans is not enabled for human patients because there are considerable evolutionary and environment

differences between humans and C. elegans. The state of the art at the time of filing was such that when food is scarce, a reversible arrest of development is triggered in C. elegans leading to the development of metabolically less active dauer larval stage which exhibit a marked increase in longevity that is also affected by the temperature (Kimura et al, Science 277: 942-946, 1997; see page 942 col.1, par.1. Larsan et al, Genetics 139:1567-1583, 1995; see page 1577, table-4, *refs of record*). However, the effect of caloric restriction on aging in humans is more complex than C. elegans because the process of ageing in humans is not only governed by various etiological factors but is also influenced by the industrialized world, modern hygiene and health care facilities (Austad, Neurobiology of Ageing 16(5):851-852, 1995, see page 851 col.2 par.3, *ref of record*). Therefore, it is unclear how the one skill in the art would conclude that administration of a compound that increases PTEN expression or activity alone would result in increased longevity in a patient.

The scope of instant invention encompass the diagnosis and treatment of all of impaired glucose tolerance, obesity and decreased longevity conditions associated with any and all environmental and genetic factors. Furthermore, the genetic interaction among various DAF genes is complex and is only well studied in C. elegans. At best the applicant's response and the specification as filed only teach PTEN-associated impaired glucose tolerance, obesity and decreased longevity in C. elagans. The specification fails to disclose the role of PTEN in all types of impaired glucose tolerance condition or obesity or propensity thereto and decreased longevity in humans, wherein other etiologic, genetic and environmental factors are involved (*e.g. ob gene, personal life style and dietary habits*). It is unclear how one skill in the art would use the invention as claimed without excessive and undue amount of experimentation to diagnose or treat impaired glucose tolerance, obesity and longevity conditions that are not regulated PTEN or daf-18 genes.

Thus, in view of the lack of guidance provided in the specification and unpredictability in the art, the skilled artisan at the time of filing would have to engage in undue amount experimentation to explore the role of PTEN modulating compounds in the treatment of impaired glucose tolerance, obesity and/or decreased longevity unrelated to DAF-18 or PTEN expression.

The quantity of experimentation required would further included the characterization of mammalian PTEN signaling pathway and its role in the onset of impaired glucose tolerance, longevity or obesity and correlation in all mammals.

Conclusion

Claims 1-5, 8, 10-17, 23, 25-28 are allowable.

Claims 18-22 stand rejected.

Claims 1-5, 8, 10-23, 25-28 are free of prior art. The prior art at the time of filing does not tech or suggest a method for the identification of compound that modulates the expression or activity of daf-18, or human PTEN genes, wherein the compound is the candidate compound for treating impaired glucose tolerance condition, obesity or capable of increasing the longevity in a cell, organism or a patient.

This is a CPA of applicant's earlier Application No. 09/205,658. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however,

event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377. If the claims are amended canceled and/or added the applicants are advised to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)*.

S. Kaushal, AU 1633

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